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㉒ Ring-contracted macrolides.

㉓ Novel 12-membered lactone and 11-membered lactone derivatives of erythromycin, having antimicrobial activity against certain Gram-positive pathogens such as Streptococcus pyogenes and Gram-negative cocci such as Haemophilus influenzae, and useful as intermediates to other macrolide derivatives, are disclosed.

EP 0 382 472 A2

RING-CONTRACTED MACROLIDES

This invention relates to novel macrolide antibiotics, which are 12-membered lactone and 11-membered dilactone derivatives of erythromycin, and to the salts and ester derivatives of these compounds.

New, improved antibiotics are continually in demand. In addition to antibiotics which are useful for treating human diseases, improved antibiotics are also needed in the veterinary field. Increased potency, expanded spectrum of bacterial inhibition, increased *in vivo* efficacy, and improved pharmaceutical properties (such as greater oral absorption, higher blood or tissue concentrations, longer body half life, and more advantageous rate or route of excretion and rate or pattern of metabolism) are some of the goals for improved antibiotics.

The macrolide antibiotic erythromycin has been the subject of much study, and a number of interesting derivatives such as erythromycylamine, 6-O-methylerythromycin and 8-fluoroerythromycin have been prepared. Making changes in the size of the macrolide ring itself, however, has not been extensively reported. Thus, it was quite surprising to discover methods for making the ring-contracted erythromycin derivatives of this invention.

The new ring-contracted derivatives of this invention have the structure shown in the formula 1.

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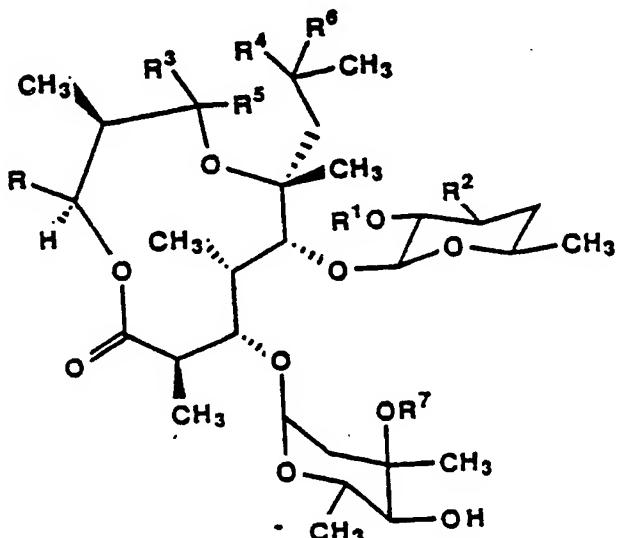
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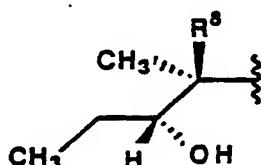
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wherein
R is (a)



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or (b) acetyl;

R¹ is hydrogen or C₁-C₅-alkanoyl;

R² is -N(CH₃)₂ or -N(CH₃)₂-O; and

50 either

a) R⁵ and R⁶ taken together form a bond, and R³ and R⁴ are 1) either both hydroxyl or 2) taken together form a bond; or

b) each of R³ and R⁵ taken together and R⁴ and R⁶ taken together form a keto group;

R⁷ is hydrogen or methyl; and

R^8 is hydrogen or hydroxyl; provided that, 1) when R is an (a) group and R^2 is $-N(CH_3)_2$, both R^3 and R^4 together and R^5 and R^6 together cannot form a bond; and 2) when R^7 is methyl, R^8 must be hydrogen; and their salts.

Thus, one group of formula 1 compounds has formula 1a

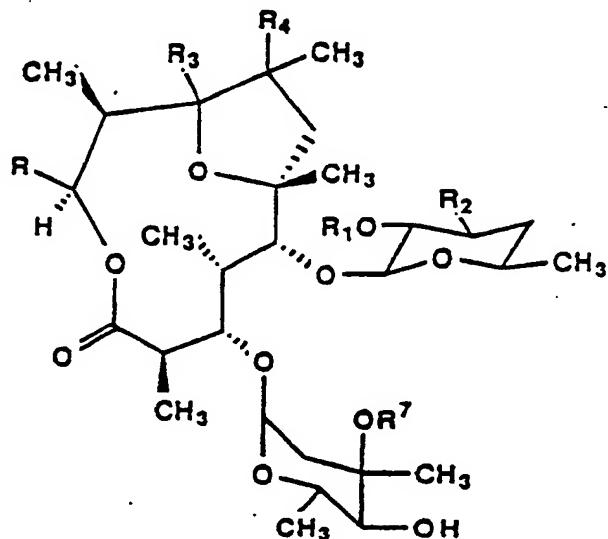
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1a

wherein R , R^1 , R^2 , R^7 and R^8 are as defined, and R^3 and R^4 are either both hydroxyl or taken together form a bond; provided that, 1) when R is an (a) group and R^2 is $-N(CH_3)_2$, R^3 and R^4 must both be hydroxyl; and

2) when R^7 is methyl, R^8 must be hydrogen; or a salt thereof.

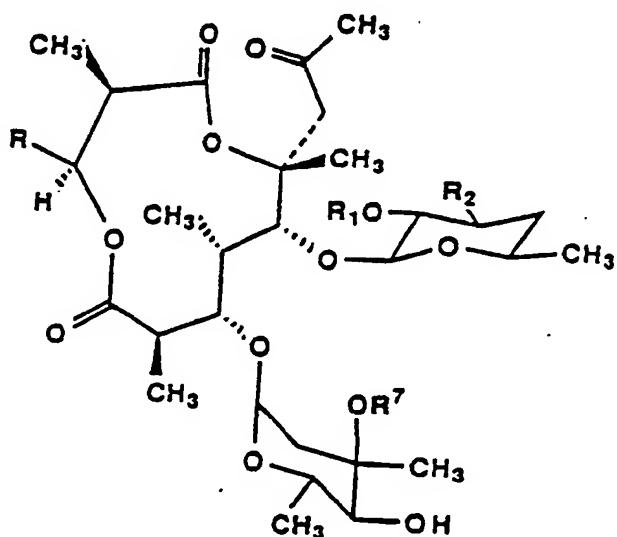
The other group of formula 1 compounds have formula 1b:

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1b

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wherein

R , R^1 , R^2 , R^7 and R^8 are as defined supra;

provided that, when R^7 is methyl, R^8 must be hydrogen; and their salts.

The 1a compounds shown in Figure 1 as 3a, 3b and 3c are especially preferred compounds of this invention.

Figures 1 and 2 show the reaction sequences used to prepare Formula 1a and 1b compounds, respectively. In Figs. 1-2, erythromycin is abbreviated "EM" and m-chloroperbenzoic acid is abbreviated "MCPBA".

Four erythromycin factors are known, erythromycins A, B, C and D. The compounds of this invention relate to derivatives of erythromycins B, C and D. In Figs. 1 and 2, the corresponding structures of the erythromycin A derivatives are included for comparison purposes.

Acid-catalyzed conversion of erythromycin to its 8,9-anhydro-6,9-hemiketal derivative (compound 2) is well known. The lactone carbonyl group in this enol ether derivative (2) can migrate from the C-13 hydroxyl to the C-11 hydroxyl group under a wide variety of reaction conditions to yield a 12-membered ring enol ether derivative (see Figure 2 - compound 3). This trans-lactonization process occurs under a variety of both acidic and basic conditions as well as thermally (in refluxing toluene). Furthermore, the acyl migration is reversible in many of these cases, so that an equilibrium between compounds 2 and 3 is established.

This invention relates to the discovery that these reactions can be applied successfully in the corresponding erythromycin factors B, C and D.

A preferred method for preparing 3 type compounds from 2 type compounds uses potassium carbonate in refluxing methanol. This method gives a mixture of 3 type compound and 2 type compound in a ratio of approximately 6:1; however, isolation of the 3 type compound on a multi-gram scale is relatively easy, using well known procedures such as extraction and chromatography.

Trans-lactonization using potassium carbonate in refluxing methanol has been confined to the 2 type enol ether compound. Erythromycin itself as well as erythromycylamine, erythromycin-9-hydrazone, erythromycin anhydro-6,9;9,12-spiroketal and 9-dihydroerythromycin all failed to give any detectable conversion to ring-contracted products.

The transformation of a 2 type compound to a 3 type compound has been accomplished by conditions as diverse as 1) potassium carbonate in refluxing toluene or tetrahydrofuran (THF), 2) triethylamine in refluxing methanol, 3) 9-borabicyclo[3.3.1]nonane (9-BBN) in THF, 4) mercuric acetate in methanol and 5) iron penta carbonyl in refluxing toluene, with trans-lactonization being the only apparent reaction.

The formula 1 compounds wherein R is acetyl are prepared by selectively cleaving the diol tail from those formula 1 compounds wherein R is (a). Selective cleavage can be accomplished using lead tetracetate in inert solvents such as toluene.

The formula 1 compounds wherein R₂ is $-N(CH_3)_2 \rightarrow O$ are prepared by oxidizing the formula 1 compounds wherein R₂ is $-N(CH_3)_2$. Hydrogen peroxide or peracids such as m-chloroperbenzoic acid (MCPBA) are preferred oxidizing agents. The reverse transformation, i.e. $-Nme_2 \rightarrow O$ to $-Nme_2$, can be achieved by reducing agents such as phosphorous(III) reagents (e.g. triphenylphosphine and tributyl-phosphine) or trialkylboranes (e.g. (sec-Bu)₃B).

The compounds of formula 1a wherein R³ and R⁴ are both hydroxyl are prepared by oxidizing the double bond in those formula 1a compounds wherein R³ and R⁴ together form a bond. Suitable oxidizing agents for this reaction are bromine, N-bromosuccinimide or N-chlorosuccinimide in solvents such as aqueous acetonitrile.

The compounds of formula 1b wherein R is (a), R¹ is hydrogen and R² is $-N(CH_3)_2 \rightarrow O$ (compound 5-type compounds) are prepared by treating a ring-contracted enol ether 3 type compound with m-chloroperbenzoic acid in dichloromethane at 0 °C. This reaction gives a mixture of products from which the 11-membered-ring diolide N-oxide can be isolated as the principal component, albeit in low yield.

The compound of formula 1b wherein R is acetyl, R¹ is hydrogen and R² is $-N(CH_3)_2$ are prepared by treating a 3 type compound with sodium periodate in aqueous acetonitrile.

The derivatives of this invention wherein R² is $-N(CH_3)_2$ can form salts, particularly acid addition salts. These acid addition salts are also useful as antibiotics and are a part of this invention. In another aspect, such salts are useful as intermediates, for example, for separating and purifying the derivatives. In addition, the salts have an improved solubility in water.

Representative suitable salts include those salts formed by standard reactions with both organic and inorganic acids such as, for example, sulfuric, hydrochloric, phosphoric, acetic, succinic, citric, lactic, maleic, fumaric, palmitic, cholic, pamoic, mucic, D-glutamic, D-camphoric, glutaric, glycolic, phthalic, tartaric, formic, lauric, stearic, salicylic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic, and like acids.

Pharmaceutically acceptable acid addition salts are an especially preferred group of salts of this invention. Pharmaceutically acceptable acid addition salts are those salts useful in the chemotherapy of a warm-blooded animal.

The compounds of formula 1 wherein R¹ is C₁-C₅-alkanoyl are prepared by esterifying the appropriate 1 compounds wherein R¹ is hydrogen by treatment with acylating agents, using standard methods well exemplified in the art (see, for example, Baltz et al. in U.S. Patent 4,321,361).

5 The new derivatives of this invention have antibacterial activity, but should be most valuable as intermediates to novel antibacterial agents.

The formula 1 compounds inhibit the growth of certain pathogenic bacteria, especially Gram-positive bacteria and Gram-negative cocci such as Haemophilus influenzae. Table I summarizes the minimal inhibitory concentrations (MIC's) at which a typical formula 1 compound inhibits certain organisms, as determined by standard agar-dilution assays.

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Table I:

Antibiotic Activity of a Formula 1 Compound ^a		
	Organism	Compound 3a ^b
15	<u>Staphylococcus aureus</u> X1.1	64
	<u>Staphylococcus aureus</u> V41 ^c	---
20	<u>Staphylococcus epidermidis</u> 270	64
	<u>Staphylococcus epidermidis</u> 222	64
	<u>Streptococcus pyogenes</u> C203	64
	<u>Streptococcus pneumoniae</u> Park 1	64
	<u>Streptococcus</u> sp. X66	64
25	<u>Streptococcus</u> sp. group D 2041	64
	<u>Haemophilus influenzae</u> C.L. ^d	128
	<u>Haemophilus influenzae</u> 76 ^e	128

^aMIC's in mcg/mL

^bCompound number from Figure 1

^cPenicillin-resistant strain

^dAmpicillin-sensitive strain

^eAmpicillin-resistant strain

35 This invention also includes 1) a formula 1 compound, or a pharmaceutically acceptable salt thereof, for use in inhibiting bacteria and 2) pharmaceutical formulations which comprise as an active ingredient, a formula 1 compound, or a pharmaceutically acceptable salt thereof, associated with one or more pharmaceutically acceptable carriers.

40 The following examples are provided in order to illustrate this invention.

Product purification by chromatography was performed on silica gel, using either flash chromatography techniques (E. Merck grade 60 silica gel, 230-400 mesh) or a Waters Model 500 Prep LC system.

Compounds were purified to homogeneity according to thin layer chromatographic (TLC) and proton NMR analyses.

45

Preparation 1

50 8,9-Anhydro-erythromycin-6,9-hemiketal (Compound 2)

55 A solution of erythromycin (20.0 g, 27.3 mmol) in glacial acetic acid (100 ml) was stirred at room temperature for 1 hour. Sodium hydroxide 5N was slowly added until precipitation was complete after the mixture had cooled back to ambient temperature. The mixture was extracted twice with dichloromethane. The combined organic layers were extracted with saturated sodium bicarbonate solution, dried (sodium sulfate), filtered and evaporated. The crude product (18.9 g) was purified by preparative HPLC (linear gradient of dichloromethane to 7% methanol + 0.5% ammonium hydroxide in dichloromethane) to yield

Compound 2 (13.2 g, 68%) as a white solid.

Preparation 2

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Preparation of 8,9-Anhydro-erythromycin B-6,9-hemiketal (Compound 2a)

10 A solution of erythromycin B (1.0 g, 1.4 mmol) in glacial acetic acid (10 mL) was stirred at room temperature for 6 hours, and the solution was evaporated to dryness in vacuo. The residue was dissolved in CHCl₃ (100 mL) and extracted with saturated NaHCO₃ solution (3 x 100 mL). The crude product was purified by silica-gel chromatography, eluting with a linear gradient of CH₂Cl₂ to CH₂Cl₂/MeOH/NH₄OH (92.5:7.5:0.5) to give compound 2a (301 mg, 31% yield) as a white solid foam.

15 IR(CHCl₃): 1720 cm⁻¹
MS(FD): m/z = 699 (M⁺)

20

Preparation 3

Compound 3 from Trans-lactonization of Compound 2

25 Compound 2 (10.0 g, 14 mmol) in methanol (200 mL) was treated with potassium carbonate (1.9 g, 14 mmol), and the mixture was refluxed for 90 min. Solvent was evaporated under reduced pressure, and the residue was partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic layer was evaporated to give 9.6 g of a white foam. This foam was purified by preparative HPLC (linear gradient of dichloromethane to 7.5% methanol + 0.5% ammonium hydroxide in dichloromethane) to yield 30 Compound 3 (5.4 g, 54%) as a white solid. FDMS m/e 715 (M + H).

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Preparation 4

Compound 4 from Lead Tetraacetate Cleavage of Compound 3

40 Compound 3 (2.0 g, 2.8 mmol) was dissolved in toluene (80 ml) and treated with lead tetra-acetate (1.9 g, 4.2 mmol). After being stirred at room temperature for 50 min., the heterogeneous mixture was extracted twice with saturated sodium bicarbonate solution, dried (sodium sulfate), filtered and evaporated. The crude product (1.8 g) was separated by flash chromatography, eluting with a gradient of dichloromethane to dichloromethane-methanol-ammonium hydroxide (96:4:0.5), to give compound 4 (780 mg, 43%) as a white foam. FDMS m/e 655 (M + H); IR 1720 cm⁻¹ (ketone carbonyl).

50

Preparation 5

Compound 5 from N-Oxidation of Compound 3

55 Compound 3 (100 mg 0.14 mmol) was dissolved in acetonitrile (1 ml) and water (0.5 ml) and then treated with 30% Hydrogen peroxide (0.014 ml) dropwise. The reaction was stirred at room temperature for 2 days, during which a white solid precipitated. The heterogeneous mixture was partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic layer was dried (sodium sulfate) and evaporated to give 60 mg (59%) of Compound 5. ¹H NMR was like that of Compound 3 except: δ 4.45-

(1'), 3.76(2'), 3.39(3'), 1.96/1.38(4'), 3.59(5'), 1.27(5'-CH³), 3.20(NMe²); FDMS m/e 731 (M + H).

Preparation 6

5

Compound 6 from Oxidation of Compound 3

10 Compound 3 (100 mg 0.14 mmol) was dissolved in acetonitrile (1 mL) and water (0.5 mL) and cooled to 0 °C for 15 min. A solution of bromine (23 mg, 0.14 mmol) in water (1 mL) was added dropwise. After being stirred for 20 min. at 0 °C, the reaction mixture was partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic layer was dried (sodium sulfate), filtered and evaporated to give 85 mg of Compound 6 (81%) as a white solid. FDMS m/e 749 (M + H).

15

Preparation 7

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Diolide 7 from MCPBA Cleavage of Compound 3

Compound 3 (1.0 g 1.4 mmol) was dissolved in dichloromethane (10 mL) and cooled at 0 °C for 30 min. A solution of m-chloroperbenzoic acid (80%, 870 mg, 0.42 mmol) was added dropwise to the cooled solution. Since conversion was incomplete after 2 hr. at 0 °C (TLC), additional m-chloroperbenzoic acid (435 mg, 0.21 mmol) in dichloromethane (5 mL) was added. After an additional 2 hr., no change was apparent by TLC. The mixture was extracted with 10% sodium bisulfite solution and then with saturated sodium bicarbonate solution. The organic layer was dried (sodium sulfate) and evaporated to give 390 mg of crude product, from which 98 mg (9%) of Compound 7 was obtained by crystallization from dichloromethane. FDMS m/e 764 (M + H); IR 1723 cm⁻¹ (lactone carbonyl).

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Preparation 8

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Diolide 8 from Sodium Periodate Cleavage of Compound 3

Compound 3 (100 mg 0.14 mmol) was dissolved in methanol (1 mL) and water (0.5 mL). Sodium periodate (240 mg, 1.12 mmol) was dissolved in water (3 mL), with the aid of sonication and methanol (2 mL) and was then added dropwise, yielding a white precipitate. After stirring the heterogeneous mixture for 11 days at room temperature, it was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The crude product (60 mg) was purified by flash chromatography, eluting with a gradient of dichloromethane to dichloromethane - methanol (23:2), to yield Compound 8 (45 mg, 47%) as a colorless glass. FDMS m/e 687 (M+); IR 1727 cm⁻¹ (lactone carbonyl).

45

Example 1

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Compound 3a from Translactonization of Compound 2a

55 Compound 2a (1.0 g, 1.4 mmol) was reacted as described in Preparation 3 to give compound 3a (845 mg, 85%) as a white solid foam.
IR(CHCl₃): 1701 cm⁻¹
MS(FD): m/z = 699(M⁺)

Table II. Proton NMR Chemical Shifts of
Macrolide Derivatives^{a,b}

Position	<u>2</u>	<u>3a</u>
2	2.74	2.78
3	4.09	4.24
4	1.88	1.70
5	3.89	3.68
7	2.65/1.97	2.76/2.02
10	2.79	2.79
11	3.47	4.72
12	--	1.62
13	4.86	3.20
13-CH ₂	1.88/1.47	1.58/1.31
13-CH ₃	0.88	0.89
2-CH ₃	1.15	1.23
4-CH ₃	1.10	1.08
6-CH ₃	1.35	1.42
8-CH ₃	1.57	1.54
10-CH ₃	1.06	1.04
12-CH ₃	1.06	0.88

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Table II. Proton NMR Chemical Shifts of
Macrolide Derivatives^{a,b} (Continued)

<u>Position</u>	<u>2</u>	<u>3a</u>
1'	4.44	4.33
10 2'	3.21	3.20
3'	2.44	2.46
15 4'	1.68/1.26	1.66/1.23
5'	3.52	3.47
5'CH ₃	1.24	1.22
N(CH ₃) ₂	2.29	2.27
1"	5.09	4.87
20 2"	2.41/1.60	2.36/1.54
4"	3.06	3.00
5"	4.09	4.04
25 5"-CH ₃	1.32	1.23
3"-CH ₃	1.26	1.32
3-OCH ₃	3.36	3.28
30 OH	3.09	NA
4"--OH	2.19	NA

35 a Obtained in deuteriochloroform solution using a
 Bruker WM-270 NMR spectrometer; chemical shifts are
 reported in parts per million from internal tetra-
 methylsilane.

40 b Number of the carbon atoms corresponds to their
 respective initial positions in 2.

45 c NA means not assigned

Table III. C-13 NMR Chemical Shifts of
Macrolide Derivatives^{a,b}

	<u>Position</u>	<u>2</u>	<u>3a</u>
5	1	1.78.30	176.30
10	2	44.82	46.82
15	3	76.59	80.55
20	4	43.28	38.98
25	5	80.26	81.79
30	6	85.63	85.95
35	7	42.69	43.49
40	8	101.47	101.53
45	9	151.78	149.80
50	10	30.47	31.29
	11	70.89	78.42
	12	75.41	38.27
	13	78.28	70.91
	13-CH ₂	21.07	26.66
	13-CH ₃	10.58	11.16
	2-CH ₃	13.50	15.34
	4-CH ₃	8.72	9.35
	6-CH ₃	26.23	26.93
	8-CH ₃	11.83	11.02
	10-CH ₃	14.81	8.99
	12-CH ₃	16.17	7.96
	1'	102.99	104.12
	2'	70.48	71.08
	3'	65.88	65.36
	4'	28.83	28.86
	5'	68.81	69.01
	5'-CH ₃	21.30	21.26
	N(CH ₃) ₂	40.33	40.30

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Table III. C-13 NMR Chemical Shifts of
Macrolide Derivatives^{a,b} (Continued)

<u>Position</u>	<u>2</u>	<u>3a</u>
1"	94.77	97.39
2"	34.73	35.32
3"	73.05	72.47
4"	78.21	78.18
5"	65.60	65.36
15 5"-CH ₃	18.25	21.51
3"-CH ₃	21.56	18.43
3"-OCH ₃	49.50	49.38

a Obtained in deuteriochloroform solution using a Bruker WM-270 NMR spectrometer; chemical shifts are reported in parts per million using internal chloroform (77.0 ppm).

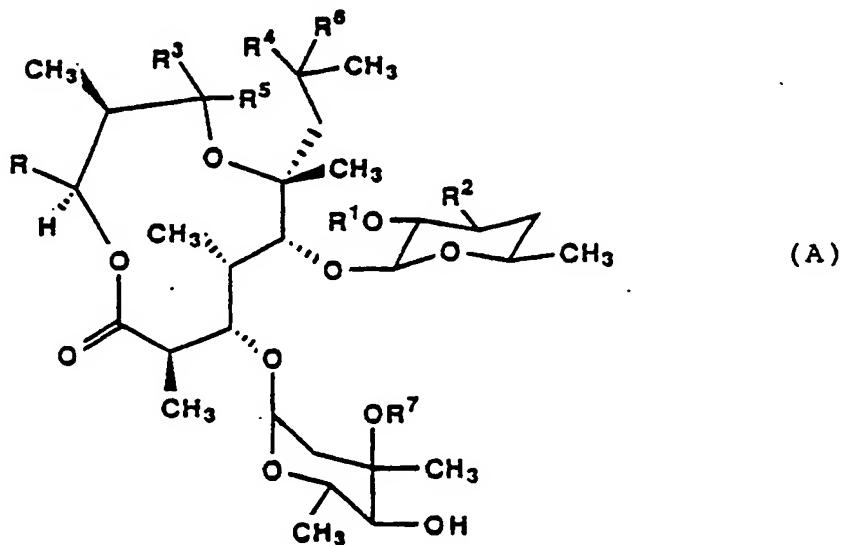
b Number of the carbon atoms corresponds to their respective initial positions in 2.

c NA means not assigned.

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Claims

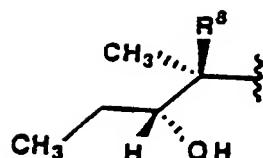
1. A compound of the formula (A)



wherein

R is a)

5



10

or b) acetyl;

R¹ is hydrogen or C₁-C₅-alkanoyl;

R² is -N(CH₃)₂ or -N(CH₃)₂-O-; and

15 either

a) R⁵ and R⁶ taken together form a bond, and R³ and R⁴ are 1) either both hydroxyl or 2) taken together form a bond; or

b) each of R³ and R⁵ taken together and R⁴ and R⁶ taken together form a keto group;

R⁷ is hydrogen or methyl; and

20 R⁸ is hydrogen or hydroxyl;

provided that, 1) when R is an (a) group and R² is -N(CH₃)₂, both R³ and R⁴ together and R⁵ and R⁶ together cannot form a bond; and 2) when R⁷ is methyl, R⁸ must be hydrogen; or a salt thereof.

2. A compound of claim 1 wherein R⁵ and R⁶ form a bond.

3. A compound of claim 1 wherein each of R³ and R⁵ taken together and R⁴ and R⁶ taken together

25 form a keto group.

4. A compound of claim 1 or 2 wherein R³ and R⁴ together form a bond.

5. A compound of claim 1, 2, 3 or 4 wherein R is an (a) group.

6. A compound of claim 1, 2, 3 or 4 wherein R is acetyl.

7. A compound of claim 1, 2, 3, 4, 5 or 6 wherein R² is -N(CH₃)₂.

30 8. A pharmaceutical formulation which comprises as an active ingredient, a compound of formula 1, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7, associated with one or more pharmaceutically acceptable carriers therefor.

9. A compound of formula 1, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7, for use in inhibiting bacteria.

35 10. A process for preparing a macrolide of formula (A) as claimed in any one of Claims 1 to 7 which comprises:

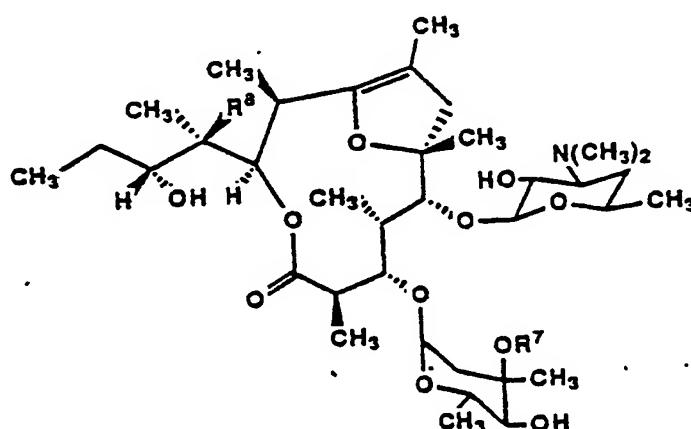
reacting a macrolide of the formula (B)

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(B)

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with

(a) an oxidizing agent such as lead tetraacetate or sodium periodate to form a formula (A) macrolide wherein R is acetyl; or

(b) an oxidizing agent such as hydrogen peroxide or a peracid to form a formula (A) macrolide wherein R^2 is $-\text{N}(\text{CH}_3)_2-\text{O}-$ or

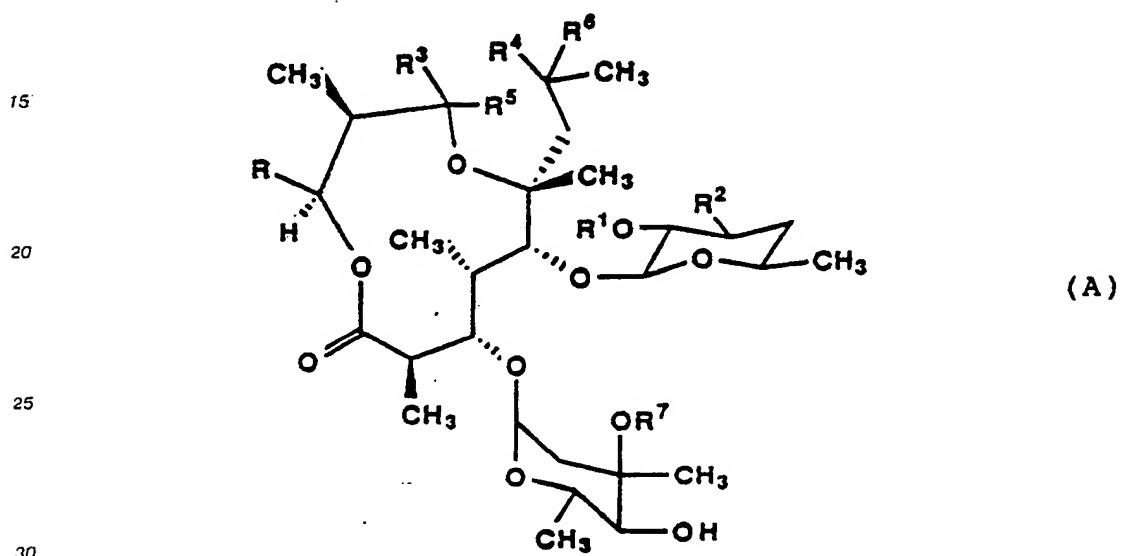
wherein R⁴ is -N(CH₃)₂-O- or
(c) an oxidizing agent such as bromine or an N-halosuccinimide to form a formula (A) macrolide
wherein R³ and R⁴ are both hydroxyl; or

5 (d) an organic peroxy acid such as a haloperbenzoic acid to form a formula (A) macrolide wherein each of R^3 and R^5 taken together, and R^4 and R^6 taken together form a keto group; or
 (e) an acylating agent to form a formula (A) macrolide wherein R^1 is C_1 - C_5 -alkanoyl.

Claims for the following Contracting States: ES, GR

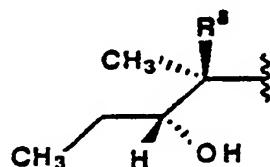
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1. A process for preparing a macrolide of formula (A)



wherein
R is a)

35



or b) acetyl;

45 R¹ is hydrogen or C₁-C₅-alkanoyl;
R² is -N(CH₃)₂ or -N(CH₃)₂→O; and

either

a) R^5 and R^6 taken together form a bond, and R^3 and R^4 are 1) either both hydroxyl or 2) taken together form a bond; or

50 b) each of R^3 and R^4 taken together and R^4 and R^6 taken together form a keto group:

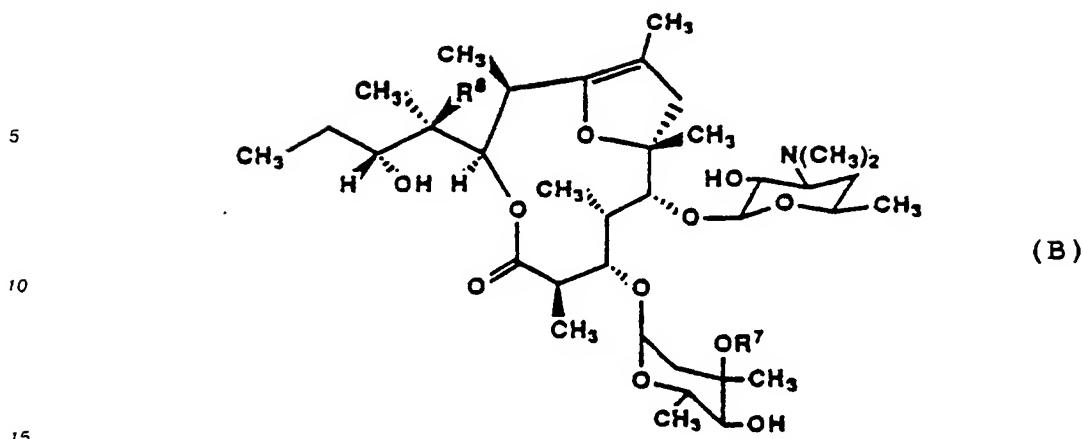
R⁷ is hydrogen or methyl; and

R⁸ is hydrogen or hydroxyl;

provided that, 1) when R is an (a) group and R² is -N(CH₃)₂, both R³ and R⁴ together and R⁵ and R⁶ together cannot form a bond; and 2) when R⁷ is methyl, R⁸ must be hydrogen;

55 which comprises:

reacting a macrolide of the formula (B)



with

(a) an oxidizing agent such as lead tetraacetate or sodium periodate to form a formula (A) macrolide wherein R is acetyl; or

20 (b) an oxidizing agent such as hydrogen peroxide or a peracid to form a formula (A) macrolide wherein R² is -N(CH₃)₂-O; or

wherein R¹ is -(C₁H₂)₂-C(=O)-C(=O)-, or
 (c) an oxidizing agent such as bromine or an N-halosuccinimide to form a formula (A) macrolide wherein R³ and R⁴ are both hydroxyl; or

(d) an organic peroxy acid such as a haloperbenzoic acid to form a formula (A) macrolide wherein each of R^3 and R^5 taken together, and R^4 and R^6 taken together form a keto group; or

(e) an acylating agent to form a formula (A) macrolide wherein R¹ is C₁-C₅-alkanoyl.

2. A process for preparing a pharmaceutical formulation which comprises admixing a compound of formula (A), or a pharmaceutically acceptable salt thereof, as defined in Claim 1, with one or more pharmaceutically acceptable carriers therefor.

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Figure 1

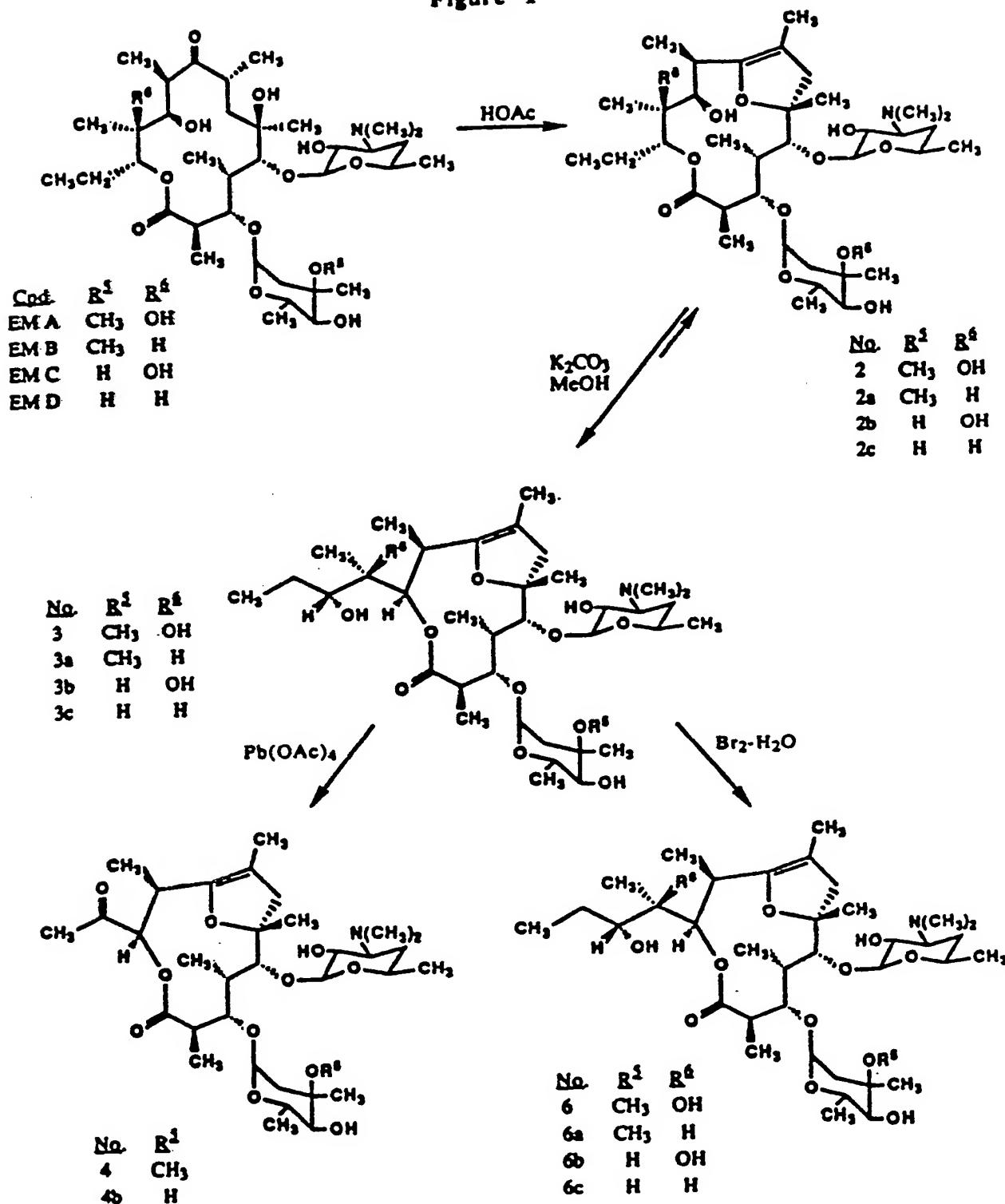


Figure 2

